

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DK62436PC/hen	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2005/002437	International filing date (day/month/year) 08/03/2005	(Earliest) Priority Date (day/month/year) 08/03/2004
Applicant  DKFZ		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 10 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐

With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐

**Certain claims were found unsearchable** (See Box II).

3. ☒

**Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

b. ☒

none of the figures is to be published with the abstract.

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international application No.  
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## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3 (in part), 8-18 (in part)

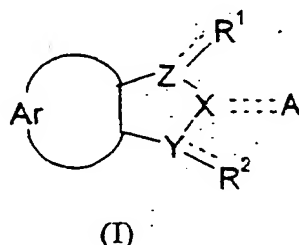
All subject-matter except subject-matter wherein A is a C1-C3 alkyl substituted by C(O)OR18  
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2. claims: 4-18 (in part)

Subject-matter in which A is a C1-3 alkyl substituted by C(O)OR18  
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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to compounds according to the general formula



wherein the dotted lines denote a single bond which is optionally present, with 2 dotted lines denoting a double bond; wherein, in case no double bond is present and a free valence exists, this valence is occupied by H; and

wherein the symbols in particular have the following meanings:

$R^1$  and  $R^2$  are independently from each other selected from the group consisting of:

H; OH; (=O); halogens; pseudohalogens;  $NH_2$ ;  $S(O)_mR^5$ ;  $SO_2NH_2$ ;  $C(O)R^8$ ;  $C(O)OR^9$ ;  $CONH_2$ ;  $C_1$ - $C_2$ -alkyl substituted by  $NH_2$ , OH,  $S(O)_mR^5$ ;  $SO_2NH_2$ ,  $C(O)R^8$ ,  $C(O)OR^9$ ,  $CONH_2$ ;  $C_1$ - $C_2$ -alkoxy substituted by  $NH_2$ , OH,  $S(O)_mR^5$ ,  $SO_2NH_2$ ,  $C(O)R^8$ ,  $C(O)OR^9$ ,  $CONH_2$ ;

Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1, 2 or 3 heteroatoms from the group N, O and S in its cycle;

Y, Z denote independently from each other a nitrogen atom or a methylene group;

X is a nitrogen atom or a methylene group;

A is selected from the group consisting of: H; halogens and pseudohalogens; OH;  $=N(OH)$ ;  $NR^{12}R^{13}$ ;  $OSO_3^-$ ;  $S(O)_mR^{14}$ ;  $SO_2NR^{15}R^{16}$ ;  $C(O)R^{17}$ ;  $C(O)OR^{18}$ ;  $CONR^{19}R^{20}$ ;  $C(S)R^{21}$ ;  $C(S)OR^{22}$ ; unsubstituted and at least monosubstituted  $C_1$ - $C_6$ -alkyl which can carry in its chain one or more non-adjacent heteroatoms from the group nitrogen and oxygen.

These compounds are used as inhibitors of DNA methylation and therefore useful in the treatment of various forms of cancer.

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/48 C07D233/66 C07D471/04 A61K31/4035 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FINLEY, WAYNE H. ET AL: "The effects on mouse sarcoma 180 of various phthalimides and derivatives of .beta.-mercaptoethylamine and .beta.-mercaptoethanol" ALABAMA J. MED. SCI. , 1(3), 252-5, 1964, XP008033999 compounds XIV - XIX	1,2,8-18
X	WO 01/85685 A (CASTRO MORERA ANA ; MORENO MUNOZ FRANCISCO JOSE (ES); PEREZ MARTIN MAR) 15 November 2001 (2001-11-15) example 4f.	1,2,8-18

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

Date of the actual completion of the international search

14 September 2005

Date of mailing of the international search report

18.10.2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Diederer, J

## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/086078 A (UNIV VIRGINIA ; BROWN MILTON L. (US)) 31 October 2002 (2002-10-31) Compounds 5-7, 16-22, 26, 29, 32, 34, 36 (pages 23-26) Compounds 1, 51, 52, 53 (Table 1) -----	1, 2, 8-18
X	US 5 238 950 A (CLADER JOHN W ET AL) 24 August 1993 (1993-08-24) claims -----	1, 2, 8-18
X	CASWELL, LYMAN R. ET AL: "Dipole moments of some 3- and 4- substituted phthalimides and phthalic anhydrides. Influence of steric and resonance effects" JOURNAL OF ORGANIC CHEMISTRY , 39(11), 1527-31 CODEN: JOCEAH; ISSN: 0022-3263, 1974, XP002292386 compound 4, cinchomeronimide (preferred compound X) -----	1, 2, 8
X	OHKI, SADA O ET AL: "Indoles. I. Syntheses of 1-acetyltryptophan and its derivatives, and their Friedel-Crafts reaction" CHEMICAL & PHARMACEUTICAL BULLETIN , 19(3), 545-51 CODEN: CPBTAL; ISSN: 0009-2363, 1971, XP008048968 Compounds 1, 8 -----	1, 2, 8
X	CASIMIR, J. RICHARD ET AL: "Methyl 2-((Succinimidooxy)carbonyl)benzoate (MSB): A New, Efficient Reagent for N-Phthaloylation of Amino Acid and Peptide Derivatives" JOURNAL OF ORGANIC CHEMISTRY , 67(11), 3764-3768 CODEN: JOCEAH; ISSN: 0022-3263, 2002, XP002333107 compound 4f -----	1, 2, 8
A	JUETTERMANN R ET AL: "TOXICITY OF 5-AZA-2'-DEOXYCYTIDINE TO MAMMALIAN CELLS IS MEDIATED PRIMARILY BY COVALENT TRAPPING OF DNA METHYLTRANSFERASE RATHER THAN DNA DEMETHYLATION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, US, vol. 91, 1 December 1994 (1994-12-01), pages 11797-11801, XP002053722 ISSN: 0027-8424 the whole document -----	1, 9, 18

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/42294 A (CELLTECH R & D LIMITED; ARCHIBALD, SARAH, CATHERINE; MOFFAT, DAVID, FE) 30 May 2002 (2002-05-30) Intermediate 5 on page 41,42	1-6,8
X	MONIQUE CALMÈS ET AL.: "Asymmetric Synthesis of (S)-Beta2-Homoarylglycines" EUR. J. ORG. CHEM., vol. 2000, 2000, pages 2459-2466, XP002344698 Compounds 5a-d	1-6,8
X	CALMES M ET AL: "New synthesis of enantiomerically pure (S)-3-amino-2-phenyl propanoic acid via the asymmetric transformation of its racemic N-phthaloyl derivative" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 9, no. 16, August 1998 (1998-08), pages 2845-2850, XP004134459 ISSN: 0957-4166 Compound 5	1-6,8
X	KAWASHIMA, KEISUKE ET AL: JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY , 28(6), 1338-40 CODEN: JAFCAU; ISSN: 0021-8561, 1980, XP002344699 Compounds 3 and 4	1-6,8
X	SCHOENENBERGER, H. ET AL: "Studies on the reaction mechanisms of local anesthetics. Part 8. Studies on the preparation of the enantiomeric N- phthalylaminocarboxylic acids" PHARMAZIE , 31(11), 811-13 CODEN: PHARAT; ISSN: 0031-7144, 1976, XP002344700 Tabel 1, L- and D-Tryptophan (Compounds 6)	1-6,8
X	DATABASE CA CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002344762 retrieved from STN Database accession no. 125:329466 abstract & PATENT ABSTRACTS OF JAPAN vol. 1996, no. 12, 26 December 1996 (1996-12-26) & JP 08 217747 A (KIKUKAWA YASUO), 27 August 1996 (1996-08-27) abstract	1-6,8
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOLASA T ET AL: "SYNTHESIS OF THE CHROMOPHORE OF PSEUDOBACTIN, A FLUORESCENT SIDEROPHORE FROM PSEUDOMONAS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 55, no. 14, 1 July 1990 (1990-07-01), pages 4246-4255, XP000673001 ISSN: 0022-3263 compound 23	1-3,6-8
X	WHITE R L ET AL: "Thiamin Biosynthesis in Yeast. Origin of the Five-Carbon Unit of the Thiazole Moiety" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 104, no. 18, 1982, pages 4934-4943, XP002234396 ISSN: 0002-7863 Compound 7	1-3,6-8
X	K. BALENOVIC ET AL.: "Reaction of N-Disubstituted Glycyl Chlorides with Diazomethane. A new Synthesis of Some beta-Alanine Derivatives. Amino Acids. V" J. CHEM. SOC., 1951, pages 1308-1310, XP002344701 Compound IV	1-3,6-8
X	K. BALENOVIC ET AL.: "(+)-Beta-Aminobutyric Acid, the Correlation of its Configuration with that of Alpha-Amino Acids" J. CHEM. SOC, 1956, pages 3982-3984, XP002344702 (+)-Beta-Phthalimidobutyric acid (starting material in Experimental)	1-3,6-8
X	ROSHAN JUMNAH ET AL: "Synthesis of N-Protected Amino Esters via Palladium Catalysed Allylic Substitution" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 34, no. 41, 1993, pages 6619-6622, XP002124526 ISSN: 0040-4020 Compound 8 and compound 18 (preferred compound IV)	1-3,6-8

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAMMERSCHMIDT, FRIEDRICH ET AL.: "Determination of absolute configuration of .alpha.-hydroxyphosphonates by <sup>31</sup> P NMR spectroscopy of correseponding Mosher esters" TETRAHEDRON, vol. 50, no. 34, 1994, pages 10253-64, XP002292385 Compound 2e (Preferred compound VI) -----	1-3,6-8
X	COSSIO, FERNANDO P. ET AL: "Reagents and synthetic methods. 48. Triphenylphosphine dibromide and dimethylsulfide dibromide as versatile reagents for beta-lactam synthesis" TETRAHEDRON LETTERS , 26(25), 3041-4 CODEN: TELEAY; ISSN: 0040-4039, 1985, XP002292387 compound 1b or 1c (Preferred compound V) -----	1-3,6-8

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0185685	A	15-11-2001	AU 5498101 A 20-11-2001
			BR 0110734 A 04-02-2003
			CA 2408747 A1 15-11-2001
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			US 2003195238 A1 16-10-2003
WO 02086078	A	31-10-2002	CA 2444704 A1 31-10-2002
			CN 1518447 A 04-08-2004
			EP 1389103 A2 18-02-2004
			JP 2004532848 T 28-10-2004
US 5238950	A	24-08-1993	NONE
WO 0242294	A	30-05-2002	AU 1416602 A 03-06-2002
			US 2002115692 A1 22-08-2002